Frontiers in Neuroendocrinology 54 (2019) 100772

Contents lists available at ScienceDirect

Frontiers in Neuroendocrinology

journal homepage: www.elsevier.com/locate/yfrne

Stress-induced disturbances along the gut microbiota-immune-brain axis and implications for mental health: Does sex matter?

Marie-Claude Audet*

School of Nutrition Sciences, University of Ottawa, Ottawa, Ontario, Canada
Department of Cellular and Molecular Medicine, University of Ottawa, Ottawa, Ontario, Canada
The Royal's Institute of Mental Health Research, Ottawa, Ontario, Canada

ARTICLE INFO

Keywords:
Depression
Gut microbiota-immune-brain axis
Hormones
Intestinal permeability
Mental health
Pro-inflammatory cytokines
Sex differences
Stress

ABSTRACT

Women are roughly twice as likely as men to suffer from stress-related disorders, especially major depression and generalized anxiety. Accumulating evidence suggest that microbes inhabiting the gastrointestinal tract (the gut microbiota) interact with the host brain and may play a key role in the pathogenesis of mental illnesses. Here, the possibility that sexually dimorphic alterations along the gut microbiota-immune-brain axis could play a role in promoting this female bias of mood and anxiety disorders will be discussed. This review will also analyze the idea that gut microbes and sex hormones influence each other, and that this reciprocal crosstalk may come to modulate inflammatory players along the gut microbiota-immune-brain axis and influence behavior in a sex-dependent way.

1. Introduction

Sex differences are increasingly recognized as being a prominent feature of mental illnesses. For instance, the prevalence of major depression and of generalized anxiety in women is about twice as that of men (Baxter et al., 2013; Ferrari et al., 2013). An increasing body of evidence also point to the fact that stressors in rodent models elicit more pronounced depressive- and anxiety-like behaviors in females than in males (Bourke and Neigh, 2011; Dalla et al., 2005; Goodwill et al., 2018; Schmidt et al., 2018; Shepard et al., 2016; Xing et al., 2013). In addition to socioeconomic influences such as abuse or poor income (Rai et al., 2013), this female bias of mood and anxiety disorders has been primarily associated with the actions of gonadal steroid hormones and sex-linked genes, leading to sexually dimorphic features within the brain (Green et al., 2019; Marrocco and McEwen, 2016). Yet, accumulating evidence suggest that additional pathophysiological contributors are likely to be at play in the "mental health gap" between males and females.

In the past decades, a growing body of evidence has indicated that microorganisms populating the gastrointestinal tract (the gut microbiota) interact with the host brain and may play a key role in the pathogenesis of mental illnesses (Dinan and Cryan, 2017; Forsythe et al., 2016; Foster et al., 2017). Although the mechanisms underlying the communication between gut microbes and the brain have yet to be entirely uncovered, routes involving the signaling of key inflammatory molecules have been positioned as crucial channels by which gut bacteria and the brain talk to each other (Abdel-Haq et al., 2019; Arentsen et al., 2017; El Aidy et al., 2016; Kelly et al., 2015). The development of the gut microbiota-immune-brain axis, in which microbial colonization of the gastrointestinal tract, maturation of the immune system and development of the brain partially overlap, is sexually dimorphic, leading to distinct gut bacterial communities, immune-signaling pathways and neuroinflammatory processes in adult males and females (Jašarević et al., 2016; McCarthy et al., 2017). In this context, it is suggested that sex-specific disturbances along the gut microbiota-immune-brain axis could play a role in promoting distinct mental health phenotypes among men and women.

In this review, an overview of inflammatory and microbial processes altered in human depression and sex differences that exist in this regard will first be provided. Next, the possibility that sex differences in inflammatory-based depression may be linked to sexually dimorphic responses to stressor or immune challenges will be explored. Experiencing adverse events during sensitive developmental periods is an important risk factor in the promotion of stress-related disorders (Heim et al., 2008; Lupien et al., 2009) and has been shown to interfere with the establishment of gut microbial patterns (De Palma et al., 2015; Golubeva et al., 2015; Jašarević et al., 2017). In this context, the potential impacts of altering gut microbial populations during critical

* Address: School of Nutrition Sciences, Ottawa, Ontario K1H 8L1, Canada.
E-mail address: maudet3@uottawa.ca.

https://doi.org/10.1016/j.yfrne.2019.100772
Received 17 February 2019; Received in revised form 7 June 2019; Accepted 9 July 2019
Available online 11 July 2019
0091-3022/

developmental windows on the establishment of a sexually dimorphic gut microbiota-immune-brain axis and of later life illnesses that differ in males and females will be examined. Finally, the potential use of sex-based dietary or microbiota-targeted interventions for health improvements will be briefly introduced. This work will also devote a particular attention to the idea that gut microbes and sex hormones may influence each other (Flak et al., 2013; Markle et al., 2013) and that this reciprocal crosstalk may come to modulate inflammatory factors along the gut microbiota-immune-brain axis and influence mood and behavior.

2. Inflammatory activation along the gut microbiota-immune-brain axis and depressive illnesses

The contribution of inflammatory factors to the pathophysiology of depressive illnesses is now well recognized. Meta-analyses have established that circulating concentrations of pro-inflammatory cytokines (signaling molecules between immune cells), especially that of interleukin (IL)-6 and tumor necrosis factor (TNF)-α, were elevated in non-medicated depressed patients who were free of physical diseases (Dowlati et al., 2010; Liu et al., 2012). A more causal role for pro-inflammatory factors in depression comes from reports showing that treatment with interferon-α in individuals with hepatitis C or cancer elicited symptoms reminiscent of major depression (Capuron and Miller, 2004; Musselman et al., 2001). In line with the view that inflammatory activation that occurs within the brain may be particularly significant for the provocation of depressive symptoms (Miller and Raison, 2016), individuals with major depression had higher levels of IL-6 in the cerebrospinal fluid (Sasayama et al., 2013), which were positively correlated with depression severity in suicide attempters (Lindqvist et al., 2009). Likewise, non-medicated individuals with a moderate-to-severe major depressive episode had increased activity of microglia, the resident immune cells of the brain, in brain regions implicated in emotional processes, as reflected by an elevated density of the translocator protein (TSPO) (Holmes et al., 2018; Richards et al., 2018; Setiawan et al., 2015). Ordinarily expressed at very low levels in microglia, TSPO can be quantified *in vivo* upon activation of these immune cells using positron emission tomography and is thus used as a marker of neuroinflammation in humans. Importantly, however, a decrease of this marker has also been observed in individuals with mild-to-moderate depression (Hannestad et al., 2013), raising the possibility that brain inflammatory activation could be a hallmark of more severe forms of depression. Pro-inflammatory cytokines were also up-regulated in post-mortem prefrontal cortex (PFC) of individuals with major depression (Dean et al., 2010; Shelton et al., 2011), as were the pattern recognition receptors (sensor proteins expressed on immune cells) Toll-like receptor (TLR)-3, TLR-4 and TLR-7 (Pandey et al., 2019). Importantly, TSPO density in the anterior cingulate cortex (Setiawan et al., 2015) as well as IL-6 and TNF-α levels in serum (Calarge et al., 2019) were positively correlated with depression severity, again suggesting that circulating and central inflammatory activation in depressed individuals could be specific to more severe states of the illness.

The phenomenon of inflammation in depression has been related to immunogenic properties of stressors (stressors are potent risk factors for depression, especially when experienced on a chronic basis or when associated with a traumatic experience; Marin et al., 2011). Circulating levels of pro-inflammatory cytokines increased after acute social challenges (Steptoe et al., 2007) and baseline inflammatory activity was elevated in individuals chronically exposed to stressful events (Kiecolt-Glaser et al., 2003). In mice, a procedure used to elicit depressive-like behaviors that has been particularly effective in increasing plasma and brain cytokines is a naturalistic stressor in the form of social defeat (Audet et al., 2011, 2010; Menard et al., 2017). This is not to say that social stressors are uniquely capable of provoking such changes as stressors involving inescapable footshocks in rodents (which also induce depressive-like behaviors; Kim et al., 2017) increased IL-6 in the frontal cortex and hippocampus (Sukoff Rizzo et al., 2012), two regions implicated in emotional and cognitive processes (McEwen and Morrison, 2013). Similar to the cytokine increases triggered by infectious agents, those elevations elicited by acute stressors can, temporarily, contribute to host defense (Allen et al., 2012). However, when experienced on a chronic basis, cytokine activation may harm other systems (Kono et al., 2014; Rock et al., 2010). In the brain, persistent inflammation damaged microglia and neurons (de Pablos et al., 2014; Frank-Cannon et al., 2009), affected monoamine activity (Felger et al., 2013), and altered neurogenesis and neuroplasticity through cytokine actions on growth factors implicated in neuronal growth and survival (Barrientos et al., 2004; Bilbo et al., 2008; Cortese et al., 2011). It is thus not surprising that signaling pathways associated with both inflammation and neurogenesis were dysregulated in postmortem hippocampus of individuals with major depression (Mahajan et al., 2018). Thus, collateral damages linked to long-lasting neuroinflammation stemming from stressor exposure may promote an array of neurobiological complications, leading to mental illnesses.

2.1. Potential sources of inflammation in depression

It has been suggested that elevated levels of pro-inflammatory cytokines in the plasma and/or serum of depressed individuals could stem from increases in intestinal permeability resulting from stressor exposure (Kelly et al., 2015; Maes et al., 2008). Psychological stressors in human volunteers and rodent models increased intestinal permeability and facilitated the passage of bacteria or of the bacterial endotoxin lipopolysaccharide (LPS; found on the outer membrane of Gram-negative bacteria) from the intestinal lumen to systemic circulation and organs (Bailey et al., 2006; Karl et al., 2017; Söderholm et al., 2002; Vanuytsel et al., 2014; Vicario et al., 2010). In line with the view that intestinal membrane integrity may be compromised in individuals with depression, ratios of lactulose to mannitol (a marker of intestinal permeability) in non-medicated adolescent females (Calarge et al., 2019) and increased levels of intestinal fatty acid binding protein (indicative of enterocyte damage) in recent suicide attempters (Ohlsson et al., 2019) were positively correlated to severity of depressive symptoms. Serum concentrations of immunoglobulin (Ig)A and IgM against LPS from commensal microbiota (Maes et al., 2012), as well as plasma levels of 16S rDNA and expression of TLR-4 in peripheral mononuclear blood cells (Kéri et al., 2014) were also increased in medication-free individuals with depression compared to healthy controls. Likewise, individuals engaged in hostile marital interactions, a stressful environment promoting risk for depression, had higher circulating levels of LPS-binding protein (LBP; produced in response to LPS translocation), although having a history of depression itself did not affect LBP levels (Kiecolt-Glaser et al., 2018). While it has been acknowledged that the available *in vivo* markers of intestinal permeability and bacterial translocation may not be yet entirely optimal (Denno et al., 2014; Sequeira et al., 2014), these findings suggest that translocated LPS-producing bacteria and/or their products could play a role in the peripheral inflammatory activation seen in depressed individuals.

In line with this view, perturbations within the gut microbiota have been reported in individuals with major depressive disorder (Huang et al., 2018; Jiang et al., 2015; Kelly et al., 2016; Lin et al., 2017; Naseribafrouei et al., 2014; Valles-Colomer et al., 2019; Zheng et al., 2016) and more recently in those with generalized anxiety (Jiang et al., 2018). Although there is no current consensus on the specific taxa altered in depression, probably owing to the heterogeneity of populations sampled, the available findings point to depressed individuals exhibiting pro-inflammatory shifts in their gut microbiota. For instance, increased abundance of Proteobacteria and of Enterobacteriaceae, a phylum and a family of Gram-negative bacteria comprised of pathogenic LPS-producing genera, have been reported in depressed individuals compared to healthy controls (Jiang et al., 2015). It is particularly interesting that proteobacterial overgrowth also occurred upon

exposure to a chronic social stressor known to elicit depressive-like behaviors in mice (Szyszkowicz et al., 2017). An overrepresentation of LPS biosynthesis genes, derived from PICRUSt analyses of fecal microbiota samples, was also predicted in a pool of individuals with a depressive or an anxiety disorder (Stevens et al., 2018), adding support to the possibility that microbiota patterns in individuals with depression and/or anxiety may be reflective of a pro-inflammatory intestinal environment. Consistent with this view, the abundance of *Faecalibacterium*, a genus containing species with anti-inflammatory properties and established health benefits (Miquel et al., 2013; Sokol et al., 2008), was decreased in individuals with depression (Chen et al., 2018b; Jiang et al., 2015; Zheng et al., 2016). A large cohort study also demonstrated that *Dialister* and *Coprococcus*, two genera associated with greater quality of life, were consistently reduced in depressed individuals even after considering the confounding influence of antidepressant medications (Valles-Colomer et al., 2019). Importantly, *Faecalibacterium* abundance was negatively correlated with symptom severity (Jiang et al., 2015) and positively correlated with indicators of quality of life and with stool concentrations of butyrate (Valles-Colomer et al., 2019), a short-chain fatty acid known to protect intestinal barrier integrity and to reduce intestinal inflammation (Louis et al., 2014), suggesting that key anti-inflammatory bacteria could potentially protect against depression.

3. Sex-based inflammatory and microbiota phenotypes in depression

3.1. Depressed males and females have different cytokine profiles

The higher prevalence of depression in women compared to men (Ferrari et al., 2013), combined with the presence of sex differences in the establishment and maintenance of the gut microbiota-immune-brain axis (Jašarević et al., 2016), strongly suggest that inflammatory and microbial profiles in depression are sexually dimorphic. In line with this view, large cohort studies have established positive correlations between circulating levels of C-reactive protein (CRP; acute phase protein involved in immune signaling) and depression severity in currently depressed men (Ramsey et al., 2016; Vetter et al., 2013; Vogelzangs et al., 2012) or in men with a lifetime history of major depression (Ford and Erlinger, 2004), but not in their female counterparts. In community-based populations, associations between serum IL-6 levels and severe depressed mood were also stronger in older men than in older women (Penninx et al., 2003) or were apparent only in men (Häfner et al., 2011). As well, depression severity was associated with a higher production of TNF-α in healthy men volunteers but with a lower production of the same cytokine in women (Majd et al., 2018). Yet, increases in circulating levels of pro-inflammatory factors have also been positively correlated with severity of depressive symptoms in currently depressed females (Birur et al., 2017; Köhler-Forsberg et al., 2017). Unfortunately, studies examining brain TSPO density in relation to human depression have not examined the influence of sex and thus it is not clear whether inflammatory activation that occurs in the brain of depressed individuals differs among men and women. A post-mortem study conducted in individuals who committed suicide has revealed that IL-4 in the orbitofrontal cortex was increased in females whereas IL-13 was increased in males, but in this study not all the victims had been diagnosed with depression (Tonelli et al., 2008b). Correlations between cerebrospinal fluid levels of pro-inflammatory cytokines (IL-6 and TNF-α) and depressive symptoms (reduced motivation, anhedonia), were more pronounced in depressed women relative to depressed men (Felger et al., 2018), suggesting that females might be more sensitive to the depressiogenic effects of inflammation that occurs in the brain, but further studies will need to be conducted to confirm this possibility.

It is not clear from available reports on the impact of sex on the relationships between inflammatory activation and depression whether males or females are more prone to inflammation-based depression. As it has been suggested earlier (Audet et al., 2014), the increased presence of pro-inflammatory cytokines in circulation may contribute to the evolution of depressive symptoms but may also be a reflection of the distress experienced by depressed individuals, as depression would itself act as a stressor. Consistent with this possibility, a longitudinal community-based study that included 13,775 individuals has established that depressive symptoms, especially those of somatic nature, predicted an increase of CRP levels over 4 years for men, but not for women (Niles et al., 2018). In contrast, CRP levels predicted worsening of depression over 4 years for women, but not for men (Niles et al., 2018), although IL-6 levels were shown to predict future depression over 7 years in men (Huang et al., 2019). Based on these findings, the possibility exists that depression and pro-inflammatory factors may be influencing each other in a sex- but also in a time-dependent manner, thus precluding the establishment of clear sex-specific patterns when inflammatory profiles in depressed individuals are examined at a single point in time. It should also be considered that sex-specific relationships between inflammatory activation and depression may be driven by the nature of symptoms, especially as sex and cytokine differences related to depression subtypes have been reported (Karlović et al., 2012; Rodgers et al., 2016; Simon et al., 2015).

3.2. Sex-specific microbiota patterns in depression

To date, only one study has looked at sex differences in relation to gut microbiota perturbations in individuals with a stress-related disorder (Chen et al., 2018a). Compared to sex-matched healthy volunteers, drug-free females with a first depressive episode had a higher abundance of Actinobacteria whereas males had a lower abundance of Bacteroidia (Chen et al., 2018a). Some of the relationships between microbiota status and severity of depressive symptoms were also sex-specific, with abundance of *Collinsella* being positively correlated with depression severity in males and *Clostridium* XIVa, Erysipelotrichaceae incertae sedis, and *Streptococcus* being negatively correlated with depression severity in females (Chen et al., 2018a). Severity of depressive symptoms in women has also been inversely correlated with fecal levels of the short-chain fatty acids propionate and acetate, suggesting that bacteria metabolizing these products could be reduced in depressed females (Skonieczna-Żydecka et al., 2018). In a large cohort study profiling fecal microbiota based on obesity, which is often comorbid with depression (Geoffroy et al., 2014), obese females had less *Phascolarctobacterium* (linked to positive mood in humans; Li et al., 2016) compared to their sex-matched non-obese counterparts, whereas obese males had increased abundance of the pathogenic *Fusobacterium* (Gao et al., 2018). Although it is premature to interpret the significance of these sex-dependent relationships at this point, the possibility exists that some of the sex-specific relationships between inflammation and depression severity could stem from changes at the gut microbiota level, although the contribution of sex hormones in this regard cannot be ignored.

4. Could sex differences in inflammatory-based depression stem from sexually dimorphic responses to stress?

Similar to what is observed in human depression, meta-analyses have established that circulating levels of pro-inflammatory cytokines, especially IL-6 and IL-1β, were increased after acute exposure to a psychological stressor in individuals exempt of infections or diseases (Marsland et al., 2017; Steptoe et al., 2007). Although no sex differences in the magnitude of stress-induced cytokine elevations have been identified in these meta-analyses, a few independent studies have shown that women displayed distinct inflammatory patterns and/or stronger inflammatory responses after stressful experiences, at least in laboratory settings. Acute exposure to a psychological stressor elicited plasma IL-1ra elevations in women, but TNF-α increases in men

(Steptoe et al., 2002). With respect to IL-6, which has been consistently linked to depressive phenotypes in both humans and animal models for depression (Dowlati et al., 2010; Hodes et al., 2014; Menard et al., 2017), stress-induced plasma increases of the cytokine were more pronounced in women than in men (Steptoe et al., 2002), although men displayed a peak in IL-6 secretion earlier than women (Edwards et al., 2006). Post-menopausal women also had higher IL-6 responses to acute stress compared to age-matched men (Endrighi et al., 2016). Greater loneliness, which may act as a psychosocial stressor (Steptoe et al., 2004) and is a strong predictor of depressive illnesses (Barger et al., 2014), was associated with more pronounced IL-6 and IL-1ra increases following a psychological stressor in women but not in men (Hackett et al., 2012). In rodents, the few studies that have included females have confirmed that brain cytokine elevations and microglial activation seen in males upon exposure to stressors that elicit depressive- and anxiety-like behaviors (Audet et al., 2011, 2010; Frank et al., 2007) also occur in females (Bollinger et al., 2016; Wohleb et al., 2018; Xu et al., 2019), although most of these changes were sex- and brain region-specific and appeared related to the type of stressors used. In addition to circulating and brain cytokine changes, the number of natural killer cells after an acute mental stressor was increased in women but decreased in men (Pehlivanoglu et al., 2012), supporting the possibility that women may be more responsive to the immunogenic effects of stressors.

In keeping with the view that stress-induced cytokine changes in circulation may stem from impairments in intestinal barrier integrity, shortly after an acute cold pain stressor jejunal permeability to macromolecules increased in women but not in men (Alonso et al., 2012). Combined with the observation that females tend to exhibit a more robust cytokine response to stressors, these findings suggest that they may be more susceptible to stress-induced activation and translocation of pathogenic microbiota, leading to cytokine secretion in circulation upon binding to their respective sensor proteins (e.g., TLRs). Consistent with this possibility, chronically stressed female mice had higher cecal abundance of Ruminococcus gnavus, a Gram-positive bacteria with pathogenic properties (Titécat et al., 2014), relative to their non-stressed controls, whereas males had a lower abundance of this bacterium (Tsilimigras et al., 2018). Unfortunately, studies that have examined the effects of stressors on potential markers of bacterial translocation have not yet included females. Plasma increases of LPS and LBP as well as brain elevations of TLR4 have been reported in male rats after exposure to acute and chronic stressors (Gárate et al., 2014, 2011). Brain TLR4 increases were prevented by antibiotics, suggesting a potential role for intestinal bacterial translocation on TLR4-signaling pathway activation upon stressor exposure (Gárate et al., 2014, 2011). It is not clear, however, whether activation of bacterial-related immune-signaling pathways upon stressor exposure would also be observed in females and/or whether they would be differently affected relative to males.

5. Are males and females responding differently to immune challenges?

Beyond inflammation elicited by non-pathogenic challenges (e.g., stressors), peripheral and central inflammatory activation that occurs in response to an immunogenic insult may also affect mood and behavior. For instance, a systemic injection of LPS in humans increased circulating levels of pro-inflammatory cytokines and TSPO density throughout the brain and promoted non-specific sickness symptoms and depressed mood (Kotulla et al., 2018; Sandiego et al., 2015). In rodents, pro-inflammatory cytokine elevations in plasma and in the brain elicited by intraperitoneal injections of LPS or of the viral mimic polyinosinic:polycytidylic acid (poly I:C) were also accompanied by sickness and depressive-like behaviors (Gandhi et al., 2007; Gibb et al., 2008). Similar to the sex-specific effects of stressors on cytokines and mood, infections (both viral and bacterial) and vaccination triggered stronger inflammatory responses and worse sickness outcomes in women than in men (Engler et al., 2016; Furman et al., 2014), although it should be noted that in a few rodent studies increased sickness behaviors in LPS-treated males compared to females have been reported (Cai et al., 2016; Pitychoutis et al., 2009). Oral and intranasal administration of LPS in mice upregulated IL-6 expression in the jejunum (Fields et al., 2018) and in the hippocampus (Tonelli et al., 2008a), respectively, in females but not in males, indicating that sexually dimorphic inflammatory responses to LPS may also occur in the intestine and in the brain. How these sex-specific inflammatory actions of LPS at the intestine and brain levels occur, however, is not entirely certain. Treatment with the nonsteroidal anti-inflammatory drug indomethacin altered fecal microbial diversity and composition in women but not in men, suggesting that their gut environment might be more sensitive to inflammatory disruptions (Edogawa et al., 2018). In line with this view, women with metabolic syndrome (which has been linked to inflammatory disturbances) had lower abundance of the anti-inflammatory *Faecalibacterium* compared to their male counterparts (Santos-Marcos et al., 2019). In relation to brain cytokines, LPS-induced increases in female mice could be related to female-specific blood-brain barrier (BBB) damages caused by the endotoxin. In support of this possibility, BBB impairments elicited by LPS were more pronounced in female than in male mice (Erickson et al., 2018), although in this study BBB damages were linked to higher cytokine levels in blood, but not in brain (Erickson et al., 2018).

To be sure, the enhanced inflammatory response to pathogenic insults apparent in women may be beneficial in the short-term, by accelerating clearance of viral or bacterial infection (Klein et al., 2010). As it has been discussed previously, however, the ramifying effects of exaggerated inflammatory activation on brain processes may ultimately be detrimental, leading to pathological health outcomes. In line with this view, depressed mood and social disconnection experienced after acute administration of LPS were more pronounced in women than in men (Moieni et al., 2015), although comparable depression and anxiety symptoms have also been reported after a small dose of the endotoxin (Engler et al., 2016). Positive correlations between pro-inflammatory cytokine elevations and severity of depressed mood and social disconnection after LPS were apparent in women but not in men (Moieni et al., 2015). Likewise, neural activity within brain regions activated in reaction to social exclusion mediated the positive relationship between plasma IL-6 elevations and depressed mood in females injected with LPS but not in their male counterparts (Eisenberger et al., 2009). These findings, combined with the observation that female rodents exhibited more pronounced depressive phenotypes upon stressor exposure relative to males (Dalla et al., 2005; Schmidt et al., 2018; Shepard et al., 2016), suggest that females may be more sensitive to the depressionogenic effects of inflammatory activation, irrespective of the pathogenic nature of the trigger (stressor versus pathogenic microbe). Tables 1 and 2 present a summary of sex-specific inflammatory changes in relation to depression as well as stressor exposure in both human and animal populations.

It is interesting that females appear to have a healthier intestinal environment relative to males. For instance, they were shown to have lower *in vivo* intestinal permeability, higher intestinal impedance and a higher microbiota diversity compared to healthy males (Edogawa et al., 2018; Elderman et al., 2018; Org et al., 2016). Mice lacking estrogen receptor exhibited disruptions of adhesion molecules in colonic tissue (Wada-Hiraike et al., 2006) and ovariectomy in rats increased colonic permeability (Braniste et al., 2009), supporting the possibility that female hormones could promote intestinal health. The possibility exists that the healthier intestinal environment apparent in females could stem from their immune system allowing an increased presence of commensal pro-inflammatory bacteria (e.g., LPS-producers). Upon stimulation (for example, after exposure to a stressor), disturbances elicited within the microbiota environment could thus lead to stronger inflammatory responses due to the presence of these commensals. In

Table 1
Summary of inflammatory outcomes in relation to depression in males and females. ↔ = correlation; (+) = positive correlation; (−) = negative correlation; → = predicts; N/A = not assessed.

		Outcomes		Regions	References
		Males	Females		
Inflammation ↔ depression severity	Current depression	+ (CRP)	No relation	Serum/plasma	Ramsey et al. (2016)
		+ (CRP)	No relation	Serum/plasma	Vetter et al. (2013)
		+ (CRP)	No relation	Serum/plasma	Vogelzangs et al. (2012)
		+ (CRP)	No relation	Serum	Ford and Erlinger (2004)
		− (IL-12)	+ (IL-6, TNF-α)	Serum/plasma	Birur et al. (2017)
		No relation	+ (CRP)	Serum/plasma	Köhler-Forsberg et al. (2017)
		Less pronounced	+ (IL-6, TNF-α)	Cerebrospinal fluid	Felger et al. (2018)
	Healthy volunteers	+ (IL-6)	Less pronounced	Serum/plasma	Penninx et al. (2003)
		+ (IL-6, CRP)	No relation	Serum/plasma	Häfner et al. (2011)
		+ (TNF-α)	− (TNF-α)	Serum/plasma	Majd et al. (2018)
		No relation	CRP → depression	Serum/plasma	Niles et al. (2018)
		IL-6 → depression	N/A	Serum/plasma	Huang et al. (2019)
Inflammatory changes	Suicide	↑ IL-13	↑ IL-4	Orbitofrontal cortex	Tonelli et al. (2008a,b)

line with this view, estrogen-driven natural antibodies able to recognize the enteropathogenic Escherichia coli have been detected in females but not in males (Zeng et al., 2018). Curiously, females appear more sensitive than males to the immunogenic and depressiogenic effects of stressors and immune challenges. In a context where inflammatory factors are considered central to the pathogenesis of depression, this sensitivity may play a key role in the "mental health gap" between males and females.

6. Where and how does it all begin?

Vulnerability to stress-related disorders may be established during sensitive developmental periods through exposure to adverse environments, which have been shown to influence physical and mental health throughout the life-course (Heim et al., 2008; Lupien et al., 2009). Aside from other processes that may operate in this fashion, there is increasing awareness about the possibility that perturbations of gut microbial colonization patterns during critical developmental windows interfere with the establishment of pathways mediating the gut-brain crosstalk and confer increased risk for physical and mental illnesses (De Palma et al., 2015; Golubeva et al., 2015; Gur et al., 2017; McVey Neufeld et al., 2016; Provensi et al., 2019). For instance, toddlers born to mothers who had undergone high levels of stress during pregnancy had higher abundance of pathogenic bacterial taxa (e.g., Proteobacteria) and these changes were linked to the incidence of gastrointestinal symptoms and allergies (Zijlmans et al., 2015). Greater bacterial diversity in toddlers was linked to lower cognitive performance (Carlson et al., 2018) and to higher levels of Surgency/Extraversion (Christian et al., 2015), a facet of temperament that has been associated with lower depressive symptoms in children (Putnam et al., 2006), indicating that associations between microbiota and behavior may be initiated early in life. In line with the view that early life experiences may have long-term ramifying effects on adult phenotypes, adult rodents stressed during the gestational or neonatal periods exhibited depressive- and anxiety-like behaviors, which were accompanied by microbiota and cytokine changes (De Palma et al., 2015; Golubeva et al., 2015; Gur et al., 2019, 2017; O'Mahony et al., 2009). Importantly, germ-free rodents (born and raised in sterile environments and thus devoid of microbiota) displayed impairments in hypothalamic-pituitary-adrenal axis function, neurotransmission, myelination, neurogenesis, microglia activity, dendrite morphology, and barrier integrity as well as reduced anxiety- and depressive-like behaviors (Braniste et al., 2014; Diaz Heijtz et al., 2011; Erny et al., 2015; Hoban et al., 2016; Luczynski et al., 2016; Moloney et al., 2017; Neufeld et al., 2011; Sudo et al., 2004; Thion et al., 2018), indicating that the absence of microbiota from the time of conception onward interfered with the developing brain and modulated behaviors.

After the prenatal and neonatal stages, the brain undergoes a second wave of substantial changes during adolescence, making it particularly vulnerable to external stimulations. It is thus not surprising that

Table 2
Summary of inflammatory changes after stressor exposure in male and female humans and animals. N/A = not assessed.

		Outcomes		Regions	References
		Males	Females		
Humans	Acute stressor	↑ TNF-α	↑ Il-1ra, IL-6	Serum/plasma	Steptoe et al. (2002)
		Less pronounced	↑ IL-6	Serum/plasma	Endrighi et al. (2016)
		Earlier IL-6 peak		Serum/plasma	Edwards et al. (2006)
		No change	↑ natural killer cells	Serum/plasma	Pehlivanoglu et al. (2012)
	LPS	Less pronounced	↑ IL-6, TNF-a	Serum/plasma	Engler et al. (2016)
		No link	↑ IL-6 and TNF-a correlated with social disconnection	Serum/plasma	Moieni et al. (2015)
	Influenza vaccination	No change	↑ antibody response	Serum/plasma	Furman et al. (2014)
Animal models	Social defeat	↑ IL-6 (mice)	N/A	Prefrontal cortex	Audet et al. (2011)
	Inescapable shock	↑ microglia activation (rats)	N/A	Hippocampus	Frank et al. (2007)
	Physical restraint	N/A	↓ microglia activation (rats)	Medial prefrontal cortex	Bollinger et al. (2016)
	Chronic unpredictable stress	↑ CSF1 receptor expression (mice)	Less pronounced	Frontal cortex	Wohleb et al. (2018)
	Chronic cold stress	Microglia activation + ↑ IL-6 and TNF-α (mice)	Less pronounced	Hippocampus	Xu et al. (2019)
	LPS	↓ IL-6 (mice)	↑ IL-6	Jejunum	Fields et al. (2018)
		No change	↑ IL-6 (rats)	Hippocampus	Tonelli et al. (2008a,b)

adversity experienced during this period may have dramatic consequences on the development of stress-related disorders (Holder and Blaustein, 2014). In line with the view that gut microbes may act on the adolescent brain and influence behavior, manipulations disturbing gut microbial populations in adolescent rodents elicited brain neurochemical disturbances as well as anxiety-like behaviors and cognitive impairments that persisted until adulthood (Desbonnet et al., 2015; Provensi et al., 2019). Conversely, microbiota-targeted interventions administered from adolescence onward attenuated depressive-like behaviors upon exposure to an adult stressor (Mika et al., 2017). To be sure, more research is required to understand the complex and dynamic interactions between the developing microbiota and the maturing brain. Nevertheless, these findings indicate that adolescence may be a unique window during which the establishment of gut-brain pathways can be modulated and the development of adult phenotypes can be influenced. As it will be discussed in the next sections, sex hormones during adolescence are undergoing dramatic changes while the gut microbiota and brain are still being remodeled, setting the perfect conditions for vulnerabilities to emerge in the event of adversity, especially as a variety of stressors are encountered during adolescence (e.g., drug/alcohol, peer pressure, risky behaviors).

6.1. Crosstalk between gut microbes and sex hormones

It is quite striking that sexually dimorphic microbiota profiles exist in healthy adult populations, in the absence of any stimulation (Edogawa et al., 2018; Haro et al., 2016; Mueller et al., 2006). Similar to humans, male and female mice across several inbred strains exhibited differences within numerous bacterial taxa, with female mice having a more diverse intestinal microbiota than males (Elderman et al., 2018; Jašarević et al., 2017; Org et al., 2016), a finding confirmed in healthy human volunteers (Edogawa et al., 2018). Differences in the composition of the adult gut microbiota among males and females have been primarily related to the actions of sex hormones. While same-sex dizygotic twins had a comparable gut microbiota, sexually dimorphic patterns emerged in opposite-sex twin pairs after puberty (Yatsunenko et al., 2012), suggesting that sex hormones may have a greater influence than genes in the establishment of gut microbial communities in males and females. In line with this view, gonadectomy in pubescent male mice prevented the development of a typical male-based adult microbiota phenotype (Yurkovetskiy et al., 2013). Adult females that had been injected with testosterone propionate on the day of birth also had reduced microbiota diversity, suggesting that the male hormone limited the establishment of particular taxa (Moreno-Indias et al., 2016). This is not to say that microbial changes elicited by sex hormones are restricted to developmental periods preceding puberty as gonadectomy in adult male and female mice also changed gut microbial patterns (Moreno-Indias et al., 2016; Org et al., 2016). Conversely, the transfer of conventionally raised adult male microbiota to pubertal female mice increased serum testosterone levels, which shifted gut microbial composition to a male-based phenotype that persisted until adulthood (Markle et al., 2013). Levels of the testosterone precursor androstenedione were also higher in these females, suggesting that testosterone elevations resulting from the microbiota transplant were consecutive to an increase in hormone production (Markle et al., 2014). Blockade of testosterone activity using an androgen receptor blocker limited the microbial changes in females (Markle et al., 2013), confirming the capacity of testosterone to modulate the composition of the gut microbiota. Beyond demonstrating that testosterone influenced the establishment of gut microbial populations, these findings raise the intriguing possibility that gut bacteria may modulate sex hormones, although it remains unclear if transplant of female microbiota to pubertal male mice would influence oestrogen activity. That being said, fecal estradiol and progesterone levels were dramatically reduced at puberty in germ-free mice (Kamimura et al., 2019), supporting the view that gut bacteria may influence female hormone patterns. This is of crucial importance as this implies that the sex bias observed in several illnesses, including depression, could be bolstered by commensal microbiota from the host (Flak et al., 2013).

6.2. Sexually dimorphic microbiota and behavioral phenotypes resulting from insults experienced during sensitive developmental periods

Challenges that occur during critical developmental windows may interfere with the establishment of sex-based adult microbiota phenotypes, with potential impacts for later life biological and/or behavioral outcomes. As previously alluded to, the prenatal and early postnatal periods as well as adolescence are critical windows during which the nervous system and the gut microbiota are undergoing rapid and profound changes under the influence of sex hormones (Markle et al., 2014; Sisk and Zehr, 2005). It is thus not surprising that stressors encountered during these periods promote sexually dimorphic vulnerabilities to illnesses, potentially through perturbations to the developing microbiota-gut-brain axis. In mice, stress experienced during gestation (through stressor procedures administered to pregnant dams) disrupted pre-existing sex differences in colonic abundances of a number of genera in neonates (Jašarević et al., 2017, 2015). Further sex-specific microbiota changes in prenatally stressed offspring emerged at weaning, with females having higher colonic abundance of *Mucispirillum*, *Odoribacter* and *Desulfovibrio* and males having more *Dehalobacterium* and *Flexispira* (Jašarević et al., 2017). In adulthood, prenatally stressed female mice exhibited reductions in stool abundance of Bifidobacteriaceae, Rikenellacea, and S24-7 (Gur et al., 2017), whereas a reduction of *Bacteroides* and *Parabacteroides* was apparent in males (Gur et al., 2019). Consistent with the view that early life experiences may promote sexually dimorphic behavioral outcomes, female mice exposed to neonatal stress, but not their male counterparts, displayed depressive-like behaviors during adolescence which became more severe in adulthood (Goodwill et al., 2018; Schmidt et al., 2018). Anxiety-like behaviors were also increased in female mice stressed prenatally compared to their non-stressed controls (Gur et al., 2017), an effect that was not seen in males (Gur et al., 2019). It appears that not only prenatal challenges of psychological nature may lead to sex-specific microbiota and behavioral outcomes as in utero exposure to valproic acid (a mouse model for autism spectrum disorders) increased cecal levels of butyrate and of a number of genera in male offspring but not in females (de Theije et al., 2014). Likewise, prenatal challenge with poly I:C led to anxiety-like behaviors in adult male mice, but not in females (Hui et al., 2018). It has been suggested that sex-dependent mental health outcomes in prenatally challenged offspring might be related to the magnitude of pro-inflammatory cytokine elevations during pregnancy rather than to the challenge itself. In line with this view, a case-control study of human depression revealed that in utero exposure to higher maternal levels of TNF-α relative to IL-10 was linked to a lower risk of developing depression in female offspring but to a higher risk in males (Gilman et al., 2016). Whether maternal microbiota patterns during a stressful pregnancy may have comparable impacts, in parallel or in combination with pro-inflammatory changes and/or hormonal fluctuations, remain to be investigated, although altered microbiota patterns in dams stressed during pregnancy were correlated to those found in neonatal and adult offspring in a sex-specific way (Gur et al., 2017; Jašarević et al., 2017).

The profound biological and psychological changes that are taking place during adolescence have been associated with the onset of puberty, during which sex hormones are increasingly secreted and come to influence brain development (Sisk and Zehr, 2005). It is now well recognized that women are particularly sensitive to pubertal hormonal changes and that adversity experienced during adolescence and puberty makes them more at risk to develop mood and anxiety disorders (Angold et al., 1998; Hankin et al., 2007). For instance, women reported higher scores of psychological distress, depression and anxiety during adolescence compared to their male counterparts (Hankin et al.,

2007; Van Droogenbroeck et al., 2018). Adversity during adolescence also predicted depression and anxiety symptoms in young adult females but not in males (Herbison et al., 2017). In rodent models, stressors experienced during adolescence have been shown to disrupt the development of stress-related pathways in a sex-specific fashion, leading to sexually dimorphic behavioral phenotypes in adulthood. Female rats stressed during juvenility displayed depressive-like behaviors whereas males did not (Horovitz et al., 2014). Likewise, chronic exposure to stress in adolescent rats elicited depressive- and anxiety-like behaviors in adult females but not in males (Bourke and Neigh, 2011). In contrast, exposure to unpredictable chronic mild stress in adolescent mice impaired cognitive functions in males but not in females while eliciting anxiety-like behaviors in both sexes (Page and Coutellier, 2018). While it has been suggested that the heightened vulnerability to mental illnesses in females during adolescence/puberty could stem from the actions of female hormones on the developing brain, whether gut microbes are involved in this process is not yet entirely clear, as the available literature on sex-specific impacts of adolescent stress on gut microbiota patterns is surprisingly very sparse. Considering that puberty appears to be a crucial window for sex hormones and gut microbes to influence each other (Kamimura et al., 2019; Markle et al., 2013) and that stress has been shown to disrupt the gut microbiota in a sex-specific way (Tsilimigras et al., 2018), these findings suggest that adversity encountered during puberty may be crucial for the establishment of sexually dimorphic vulnerabilities to mental illnesses, through disruptions of the maturing gut-brain axis.

6.3. Perturbations of developing gut-brain signaling routes and sex-specific later life outcomes

Some of the routes mediating the gut-brain crosstalk are established during periods where molecular and cellular brain pathways crucial for mental health are also being developed (Jašarević et al., 2016; McCarthy et al., 2017; Rice and Barone, 2000), supporting the possibility that aberrant connections between gut microbes and the developing brain could predispose to mental illnesses. Our preliminary data indicated that pro-inflammatory cytokines and tight junction proteins in the small intestine and the brain differed in adult male and female mice offspring born to stressed dams (Osborne et al., 2018), in accordance with previous reports in prenatally stressed or maternally separated offspring (Bolton et al., 2013; Gur et al., 2019, 2017; Moussaoui et al., 2017, 2016). Combined with the observation that prenatal and early postnatal stressors disturb the establishment of gut microbial patterns throughout the life-course (De Palma et al., 2015; Gur et al., 2019, 2017; Jašarević et al., 2017), these findings suggest that early life experiences may compromise the development of the gut microbiota-immune-brain axis in a sex-specific fashion, with potential impacts on behavior. Whether adversity experienced during adolescence exerts comparable sex-specific effects on the developing gut microbiota-immune-brain axis is less clear. Pro-inflammatory cytokine elevations in the hippocampus in response to an LPS administered in adulthood were potentiated in males that had been stressed in adolescence but not in females (Pyter et al., 2013), supporting the view that immune routes can be sensitive to pubertal challenges in a sex-specific way.

It is now well established that in addition to their immune function in the brain, microglia actively participate in brain development, by pruning synapses, regulating programmed cell death, and driving synaptogenesis and neurogenesis in the maturing brain (Marín-Teva et al., 2004; Paolicelli et al., 2011; Shigemoto-Mogami et al., 2014; Weinhard et al., 2018). During the early postnatal period, more microglial cells within brain regions involved in cognitive processes were found in males, indicating that microglial developmental patterns are sex-specific (Schwarz et al., 2012). In early adolescence, females had more microglia with activated morphology, a pattern that persisted into adulthood where higher levels of pro-inflammatory genes were also apparent, suggesting that microglia in females may be more active from juvenility onward (Schwarz et al., 2012). As it has been alluded to previously, increased inflammatory responses in women may be beneficial in the short-term (Klein et al., 2010), but exaggerated and/or chronic brain inflammatory activation may ultimately be detrimental, leading to mental health outcomes.

In line with the view that gut microbes may play a key role in the modulation of microglia and thus modulate brain inflammatory activity, microglial cells were altered in germ-free mice (Erny et al., 2015). Microbiota-targeted interventions also decreased microglial activation and improved cognitive functioning in middle-aged mice (Boehme et al., 2019), rats fed with a high-fat diet (Chunchai et al., 2018), and mice treated with MPTP (a mouse model of Parkinson's disease) (Sun et al., 2018), suggesting that modulation of gut microbes may act on microglia and thus might possibly influence brain inflammatory activity. How these effects are taking place is still unclear but some indications point to the possibility that short-chain fatty acids may be involved (Boehme et al., 2019; Erny et al., 2015).

Microbiota profiles in healthy adult mice have been linked to colonic expression of genes related to immunological functions in a sex-specific manner (Elderman et al., 2018), supporting the possibility that developmental microbiota trajectories could differentially impact the maturation of inflammatory processes in males and females, at least in the colon. In line with the view that immune differences between males and females can be driven by gut microbes, microbiota transfer from conventionally raised males to germ-free adult females elicited increases in T-cell precursors in the thymus (Fransen et al., 2017). Together, these findings raise the possibility that the reciprocal influence between gut bacteria and sex hormones could modulate inflammatory and immune factors along the signaling routes connecting the intestine and brain environments, with potential impacts on physical and mental health (Fig. 1).

6.4. Hormone-dependent brain function in germ-free mice

Despite the accumulating evidence suggesting that microbiota and sex hormones influence each other (Markle et al., 2013; Moreno-Indias et al., 2016; Yurkovetskiy et al., 2013) and that gut microbes may play a role in the pathogenesis of depressive illnesses (Dinan and Cryan, 2017; Forsythe et al., 2016; Foster et al., 2017), it should be emphasized that not all depression-related sexually dimorphisms are dependant on gut microbes. For instance, increased levels of serotonin and its main metabolite and decreased expression of BDNF in the hippocampus were apparent in germ-free male mice but not in their female counterparts (Clarke et al., 2013). Likewise, type 1 interferon intestinal signaling pathway was more activated in germ-free female mice than in germ-free males (Fransen et al., 2017). In keeping with the view that hormone fluctuations may be more influential than gut microbes for particular outcomes, sex-specific effects on microglia vary during the development of germ-free mice, with embryonic microglia alterations being more pronounced in germ-free males and adult microglial perturbations being more marked in females (Thion et al., 2018).

7. Gut microbiota during periods of hormonal fluctuations: A recipe for mental illnesses?

In addition to puberty, remodeling of gut microbial communities have been reported during periods where drastic hormonal shifts are taking place, including pregnancy, postpartum, and menopause. For instance, Proteobacteria/Enterobacteriaceae and Actinobacteria increased over the course of pregnancy, whereas members of Clostridiales, including *Faecalibaterium*, decreased (Koren et al., 2012), although it should be noted that others have failed to report any stool microbial shifts during this period (DiGiulio et al., 2015). Transfer of human microbiota collected during the third trimester of pregnancy to germ-free female mice elicited pro-inflammatory cytokine elevations in

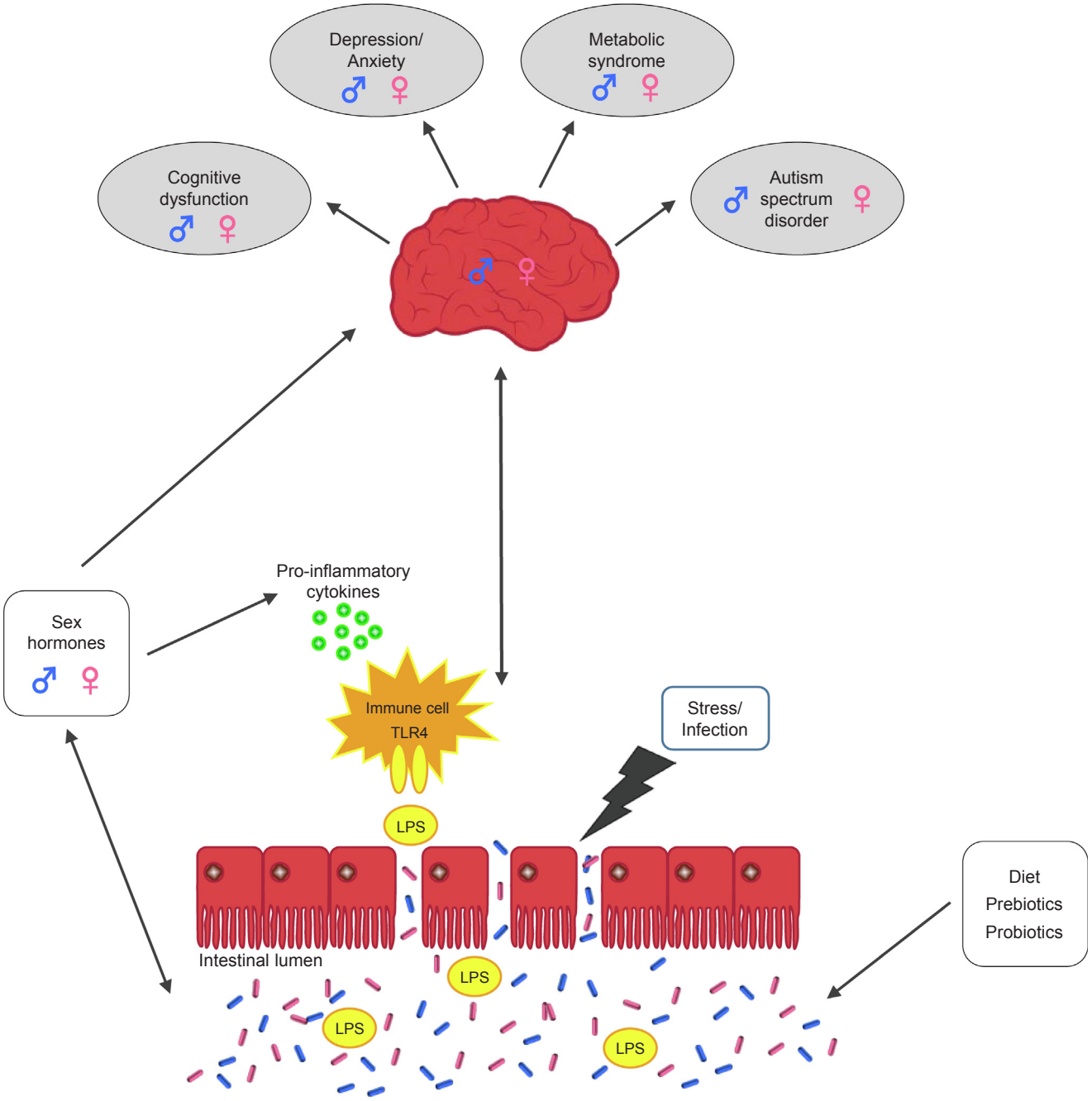

Fig. 1. Schematic representation of the potential influence of gut microbes and sex hormones on the immune-signaling routes mediating the crosstalk between the gut microbiota and the brain, ultimately leading to sexually dimorphic health outcomes. It is suggested that the reciprocal influence between sex hormones and the gut microbiota may come to modulate the gut microbiota-immune-brain axis. Elevations of the pro-inflammatory tone within the intestinal environment and damages to the intestinal barrier ordinarily elicited by stressor or immune challenges could be affected by these microbe-hormone relationships in a sex-dependent manner, with potential impacts on translocation of bacterial products (e.g., LPS) and subsequent activation of their respective signaling pathways (e.g., TLRs, pro-inflammatory cytokines). Inflammatory processes in the blood and in the brain would remain sensitive to the effects of sex hormones. In addition, it is proposed that dietary or microbiota-targeted interventions (e.g., prebiotics, probiotics) may act on the gut microbiota in a sex-specific manner, potentially through their effects on sex hormones. Ultimately, sex-specific disturbances along the gut microbiota-immune-brain axis would promote sexually dimorphic features within the brain and distinct mental health phenotypes among men and women.

stool and cecal samples (Koren et al., 2012), indicating that the microbiota changes experienced during pregnancy could be pro-inflammatory. The postpartum and menopause periods, during which abrupt reductions of female hormones occur, have also been linked to gut microbial variations. Postmenopausal women had more *Lachnospira* and *Roseburia*, less *Prevotella*, *Parabacteroides* and *Bilophila*, and higher plasma IL-6 levels compared to premenopausal women (Santos-Marcos et al., 2018). Ovariectomy in aged female rats (an animal model of menopause) reduced bacterial diversity, increased *Helicobacter* and *Anaerovorax*, and decreased *Anareotruncus* (Zhang et al., 2017), confirming that reductions in female hormones at the age of menopause altered gut microbiota composition. Perhaps not coincidentally, postpartum and menopause have been associated with an increased risk of mood and anxiety disorders in women (Cohen et al., 2006; Freeman et al., 2006).

In line with the possibility that microbial changes during pregnancy

could be mediated by the actions of female hormones, progesterone implants in female mice increased stool abundance of *Bifidobacterium* (which was found to be elevated during late pregnancy in both women and female mice), a finding replicated *in vitro* using a progesterone-enriched growth medium (Nuriel-Ohayon et al., 2019). Likewise, administration of progesterone in ovariectomized mice increased *Lactobacillus* species, decreased IL-6 expression in the cecum and improved depressive- and anxiety-like behaviors (Sovijit et al., 2019). Although the significance of the microbiota changes taking place during periods of hormonal fluctuations is not yet entirely clear, these latter findings are of crucial importance as they strongly support the possibility that female hormones may drive the growth of specific bacterial populations, which may have important implications for the understanding of the female bias of mood and anxiety disorders.

8. Could dietary interventions for health improvements be based on sex?

The effects of dietary patterns on the gut microbiota are now well recognized (David et al., 2014). It has been suggested that in addition to hormonal influences (Markle et al., 2013), sexually dimorphic microbial patterns could be linked to males and females having different diets. A very elegant study conducted in both wild and laboratory fishes and in a human population demonstrated that diet and sex interactively influenced gut microbial communities, suggesting that some of the bacteria that were sensitive to sex hormones were also responsive to foods (Bolnick et al., 2014). Consistent with the view that gut microbes may be responsive to diet in a sex-specific way, a 3-year low-fat diet intervention in individuals with metabolic syndrome increased abundance of *Desulfovibrio*, *Roseburia* and *Holdemania* in men relative to women (Santos-Marcos et al., 2019). In rats, oligofructose supplementation increased fecal levels of butyrate in males but not in females (Shastri et al., 2015), indicating that gut bacteria in males and females metabolized the prebiotic differently. Supplementation with the omega-3 acid docosahexaenoic acid in mice shifted microbiota profiles and reduced depressive- and anxiety-like behaviors in stressed males but not in their female counterparts (Davis et al., 2017), suggesting that some types of supplements may benefit one sex only, thus potentially opening the door to sex-based nutritional interventions. It should be noted, however, that being fed a high fat diet from weaning onward in female rats had less impacts on the adult gut microbiota that hormonal changes consecutive to neonatal testosterone supplementation or to adult ovariectomy (Moreno-Indias et al., 2016), indicating that sex hormones may have more influence than diet on gut microbial communities.

A few reports have indicated that probiotic strains of Lactobacillus elicited sex-specific microbiota, inflammatory and behavioral improvements in stressed or immunocompromised populations. Ingestion of a heat-inactivated strain of Lactobacillus during the examination period in students limited stress-related somatic symptoms in females and improved sleep quality and reduced diarrhea in males (Nishida et al., 2017). A probiotic mixture of five Lactobacillus strains given to lupus-prone mice re-established levels of Lactobacillales, increased tight junction protein expression and reduced IL-6 levels in the intestine of female and castrated male mice, but not in non-castrated males (Mu et al., 2017). In contrast, Lactobacillus reuteri in adult mice reduced TNF-α expression in the jejunum and ileum of males but not of females (McCabe et al., 2013). Intriguingly, supplementation with Lactobacillus reuteri in young male mice increased serum levels of testosterone and enhanced testicle size during aging compared with mice not receiving the probiotic (Poutahidis et al., 2014), suggesting that some of its sex-specific effects on inflammatory and behavioral outcomes may be mediated by its actions on sex hormones. Consistent with the view that dietary-based interventions may modulate sex hormones, intake of dietary fibers in women was inversely correlated with serum concentrations of estradiol and progesterone (Gaskins et al., 2009). Considering that gut microbes may influence sex hormones and reinforce sex differences (Flak et al., 2013; Markle et al., 2013), the selection of appropriate microbiota-based interventions for physical and/or mental health improvements will thus require careful examination.

9. Concluding remarks

Despite the dramatic increase of the psychological and economic burden attributable to depressive illnesses, approximately 30% of individuals still present symptoms after their first treatment (Rush et al., 2006; Trivedi et al., 2006). The development of effective pharmacological interventions for depression has been impeded in part by our incomplete understanding of the mechanisms underlying the illness, although it is now understood that “one-treatment-fits-all” is inappropriate, given that depressive illnesses are highly heterogeneous. Considering that women are twice as likely to develop depression than men (Ferrari et al., 2013) and that they respond differently to antidepressant treatments (Sramek et al., 2016; Williams and Trainor, 2018), a special attention needs to be given to the sexually dimorphic patterns of depression pathogenesis when developing new treatment approaches to alleviate symptoms in this population.

Unfortunately, our knowledge of sex differences in relation to depression, and more specifically to inflammatory-based depression, has been greatly impacted by the fact that human studies investigating pathophysiological processes associated with the illness have often overlooked the impact of sex. Although improvements have been seen in the past years, most of the animal studies for stress-related disorders have been focussing predominantly on males and thus have failed to thoroughly examine sex differences in the investigation of biological and behavioral phenotypes related to mental health. As it has been previously emphasised (Eid et al., 2019), there is an urgent need for preclinical and clinical research in both normal and stress conditions to be conducted in males and females to inform the development of effective evidence-based interventions to prevent the development of mental illnesses and/or attenuate symptom severity. This is of particular importance as it could potentially open the door to sex-based treatment interventions for depression and for stress-related disorders in general.

Funding

This work was partly supported by the Individual Discovery Grant #RGPIN-2016-06146 from Natural Science and Engineering Research Council (NSERC) to MCA.

Declaration of Competing Interest

None.

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Glossary

Bacterial translocation: Passage of microbes and microbial products (e.g., endotoxin) from the intestinal lumen through the epithelial mucosa into circulation and organs.

Commensal: Organism living in close association with an organism from a different species, in which one benefits from the association and the other is unaffected.

Critical/Sensitive developmental periods (or windows): Developmental stage during which an organism is especially sensitive to environmental stimuli.

Gut microbiota: Microorganisms inhabiting the gastrointestinal tract.

Gut microbiota-immune-brain axis: Immune signaling pathways mediating the relationships between gut bacteria and the brain.

Microglia: Resident immune cells of the brain.

Microbiota-targeted interventions: Manipulations aimed at changing the composition of microbial populations in the gastrointestinal tract. May include, among other manipulations, probiotics, prebiotics, or fecal transplants.

Ovariectomy: Surgical intervention of removing one of both ovaries.

Pattern recognition receptors: Sensor proteins expressed on immune cells, detecting molecules associated with microbial pathogens or cell damage/death, ultimately initiating a pro-inflammatory cascade.

Prebiotic: Substrate selectively used by host microorganisms conferring a health benefit.

Probiotic: Live microorganisms that, when administered in adequate amounts, confer a health benefit to the host.

Pro-inflammatory cytokines: Signaling molecules between immune cells.

Short-chain fatty acids: End products of dietary fiber fermentation by anaerobic gut bacteria.

Sexually dimorphic: Which differ between males and females of the same species.